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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER

MAIER, LEIGH C

ART UNIT PAPER NUMBER

1623

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/680,000

Applicant(s)

AESCHLIMANN ET AL.

Examiner

Leigh C. Maier

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1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-27 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 14-27 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/11/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Information Disclosure Statement

Although all documents listed on the IDS, filed March 11, 2004, were submitted and made of record in the parent case S.N. 09/156,829, the examiner has reviewed the file and finds that only a few of the listed non-patent literature documents were available. These have been initialed on the attached PTO-1449. If Applicant wants the remaining documents to be made of record in the present prosecution, they must be re-submitted. The examiner notes that Applicant has indicated a willingness to do so and regrets any inconvenience.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Step b) of claim 14 recites "substituting at the carbonyl carbon ... a side chain comprising a nucleophilic portion and a functional group portion." This appears to require a product that has a side chain attached to the carbonyl carbon which, after the reaction, comprises both a nucleophilic group and some other functional group. However, this is not consistent with claim 15 wherein the nucleophilic portion can be ammonia. It is not clear how ammonia is meant to be bonded to the side chain. It could be that what is intended is that step b) comprises a

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nucleophilic addition to the carbonyl wherein the resulting attached moiety comprises a functional group portion. Again that does not seem to be entirely consistent with claim 15 and the specification. Claim 15 recites hydroxyl and sulfhydryl as the “nucleophilic portion” (or nucleophile), but the specification only appears to discuss nucleophilic addition of amines that have an additional functional group portion. In view of the forgoing, one of ordinary skill would not be apprised of the metes and bounds of the claims. The claims are thus rendered vague and indefinite.

Further regarding claim 19, the term “the crosslinker” does not have a positive antecedent in the claims.

Further regarding claims 23-26, these claims limit only generic terms in claim 22, but not necessarily the overall invention. For example, claim 23 recites “wherein the bioactive peptide is RGD.” If this limitation is incorporated into claim 22, it limits the bioactive peptide that may be selected to RGD. However, it does not require that RGD be present, only that if a biopeptide is present, it must be RGD. If an art-disclosed method met all the limitations of claim 18 (from which claim 22 depends) and were performed in the presence of a growth factor, it would still anticipate claim 23 (and 24-26). It may be that what is intended is something to the effect of “The method of claim 22, wherein the bioactive peptide RGD is present.”

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14-19 are rejected under 35 U.S.C. 102(e) as being anticipated by MILLER et al (US 6,174,999).

MILLER discloses the preparation of activated esters of hyaluronic acid (HA) followed by the nucleophilic addition of multifunctional amines. The non-bound functional groups further react with activated ester sites to form a crosslinked product in the form of a gel, film or foam. See examples, particularly 25, 28, and 30.

The reference does not explicitly state that the product is crosslinked. However, with the multifunctional reagents and additional carbodiimide reaction step, it does appear that crosslinking would take place. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 14, 15, 17, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by WAKI et al (US 6,025,444).

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WAKI discloses treatment of HA with NHS and a carbodiimide. The activated ester product is then reacted with a cinnamic acid derivative. This product is cast as a film followed by UV crosslinking. In determining the degree of gelation, the film is hydrated, thus forming a crosslinked hydrogel. See example 22.

Claims 14-16 are rejected under 35 U.S.C. 102(e) as being anticipated by RIGHETTO et al (US 5,856,299).

RIGHETTO discloses the preparation of a variety of activated HA-esters. These activated esters are treated with amines, amino acids, and peptides to form conjugates. See examples.

Claims 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by AKIMA et al (EP 506976).

AKIMA discloses the treatment of HA with EDC and NHS to form an activated ester, which is then treated with aminocaproic acid. The HA/linker product is then treated with EDC to produce an activated ester functional group (the O-acylisourea) which is further reacted with daunomycin to form an HA-daunomycin conjugate. See example 2 (production example 1) at pp 10-11.

Claims 14-19 are rejected under 35 U.S.C. 102(b) as being anticipated by GUIRE et al (US 5,512,329).

GUIRE teaches the preparation of ANP-EAC-HA by treating HA with EDC and sulfo-NHS to form an activated ester followed by the addition of ANP-EAC-jeffamine. The reaction

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introduces an arylazide functional group into the HA. See col 10, lines 26-40. This product is crosslinked to form a hydrogel. See example VIII.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-19 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MILLER et al (US 6,174,999).

MILLER teaches as set forth above. The reference further suggests the dispersion of various pharmaceutically active substances, such as drugs and growth factors, in the HA composition. See paragraph bridging col 3-4. The reference does not exemplify their use. Neither

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does the reference exemplify the full range of activated esters, but they are specifically suggested. See col 2, lines 57-67.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to conduct the crosslinking reaction in the presence of these pharmaceutically active substances in order to evenly disperse them throughout the hydrogel. One of ordinary skill would reasonably expect success in doing so. In the absence of unexpected results, it would also be within the scope of the artisan to select any reactant known in the art to be useful for the preparation of an activated ester with carbodiimide coupling.

Claims 14-19 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MILLER et al (US 6,174,999) in view of PRESTWICH et al (US 5,874,417).

MILLER teaches the derivatization of HA with a variety of functional groups as set forth above. Several others not exemplified are explicitly suggested. See col 3, lines 17-27. The reference does not teach hydrazide as the functional group.

PRESTWICH teaches the functionalization of HA with hydrazido reactive groups. See abstract and col 3. The reference teaches that hydrazido groups are reactive carboxyl groups in the presence of a carbodiimide. See paragraph bridging col 4-5.

It would have been obvious to one having ordinary skill at the time the invention was made to prepare HA-derivatives by the method of MILLER comprising the use of a hydrazido functional group. One of ordinary skill would reasonably expect success in using such a group as it is reactive with activated esters and would be expected to undergo self-crosslinking as in the

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method of MILLER. Crosslinking in the presence of other substances and reactants for preparing activated esters are addressed above.

Claims 14-19 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MILLER et al (US 6,174,999) in view of STEDRONSKY et al (US 5,817,303).

MILLER teaches the derivatization of HA with a variety of functional groups as set forth above. Several others not exemplified are explicitly suggested. See col 7, lines 58-67. The reference does not teach the full scope of functional groups recited in claim 16.

The concept of functionalizing polymers to effect crosslinking is well known in the art. STEDRONSKY discusses the functionalization of biopolymers with a variety of active moieties. See col 3, lines 11-29.

It would have been obvious to one having ordinary skill at the time the invention was made to prepare HA-derivatives by the method of MILLER comprising introducing any of the functional groups known in the art to be effective for facilitating crosslinking and particularly those reactive with amine or carboxyl groups. It would be within the scope of the artisan to make such modifications with a reasonable expectation of success. Crosslinking in the presence of other substances and reactants for preparing activated esters are addressed above.

Claims 14-16, 18, 19, and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over RHEE et al (US 5,510,418) and RIGHETTO et al (US 5,856,299).

RHEE teaches the preparation of crosslinking an activate PEG to glycosaminoglycans (GAGs), with HA being exemplified. See abstract; col 14-20; and examples 1 and 2. The

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reference further suggests the inclusion of biological substances, such as cytokines, growth factors, and other drugs. Cytokines and growth factors, such as TGF- β or BMP, are included to encourage biological anchoring of the composition when administered *in vivo*. These substances may be tethered to the GAG or mixed with the composition. The compositions are useful for such methods as wound healing, osteogenesis and drug delivery. See the paragraph bridging col 11-12 and col 26, lines 54-63. Furthermore, the reference teaches that the crosslinking can be performed *in situ*. See paragraph bridging col 25-26. The reference does not exemplify a HA-derivative such as that prepared according to claim 14.

RIGHETTO teaches as set forth above. The products disclosed have utility in wound healing and tissue repair. See paragraph bridging col 5-6. The reference exemplifies the preparation of an HA-RGD conjugate and suggests a general method for attaching similarly active biomolecules. See example 15.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of RHEE by using a peptide-conjugated HA, such as the RGD derivative disclosed by RIGHETTO, for crosslinking with PEG. The artisan would be motivated to make such a modification because RHEE had suggested the use of drug conjugated GAGs, particularly HA, for this method. One of ordinary skill would reasonably expect success in making this modification. It would be further obvious to perform the crosslinking in the presence of the recited biomolecules because RHEE had suggested their inclusion, either by admixture or covalent attachment, in the composition. Finally, it would have been obvious to perform the crosslinking *in situ*, as this method was specifically taught by RHEE.

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Claims 14-16 and 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over RHEE et al (US 5,510,418) and RIGHETTO et al (US 5,856,299) in view of HUNZIKER et al (US 5,270,300) and HOHENADL et al (JBC, 1995).

RHEE teaches as set forth above. The reference further teaches compositions that further comprise collagen.

RIGHETTO teaches as set forth above.

The references do not teach crosslinking with transglutaminase or an HA conjugate of a transglutaminase substrate, such as APQQA.

HUNZIKER teaches the use of a biocompatible matrix for the repair of cartilage and bone tissue. See abstract. This reference also teaches that RGD peptides are advantageously used in materials for the repair of tissues. See col 13 lines 14-17. The reference also teaches that the adhesion of a biomaterial to cartilage can be enhanced by the addition of transglutaminase. See col 4, lines 25-33 and col 14, lines 54-58.

HOHENADL teaches BM-40-derived peptides that comprise transglutaminase amine receptor sites. See Fig. 3.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare an HA conjugate comprising a transglutaminase substrate peptide to include in the composition taught by RHEE. This conjugate would have the advantage of facilitating the attachment of the composition to cartilage surface and crosslinking to collagen by the addition of transglutaminase. It would be further obvious to select any peptide comprising a known amine acceptor site. In the absence of unexpected results, it would be within the scope of the artisan to select a useful peptide from the domains taught by HOHENADL. One of ordinary

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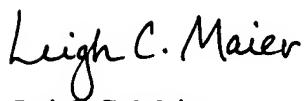
skill would reasonably expect success in using such a conjugate in the compositions taught by RHEE.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Visit the U.S. PTO's site on the World Wide Web at <http://www.uspto.gov>. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.



Leigh C. Maier
Primary Examiner
May 26, 2005